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MARCH 15, 1963

PROGRESS REPORT #6

ON

PERCUTANEOUS ABSORPTION

TO

ARMY CHEMICAL CENTER

EDGEWOOD, MARYLAND

CONTRACT #DA 18-108-405-CML-215

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PROGRESS REPORT ON PERCUTANEOUS ABSORPTION

Our efforts have been directed in three main areas:

- PART I In vitro measurement of percutaneous absorption of C^{14} labelled compounds through human skin.
- PART II Estimation of percutaneous absorption of a specific anticholinergic agent. The effect of this topical anticholinergic agent on delivery of sweat in human skin and on the development of miliaria.
- PART III In vivo studies of the existence of a reservoir in human keratin and its capacity. This reservoir is for topically applied chemical agents.

PART I:

Reference is made here to our contractor's report submitted in October 1962. This report covers some of the work between our previous progress report #5 and October 1962.

Since the report which was submitted by us in October, a number of experiments has been performed with C^{14} labelled material to measure percutaneous absorption in human skin in vitro.

Table I shows the relative penetration of lauric acid (C^{14}) when applied in different concentrations. It can be seen that the percent of lauric acid recovered (penetrated) is constant with decreasing concentrations of lauric acid applied to the surface. Also, the total amount of lauric acid penetrating is greater (proportionately) with increasing concentrations applied to the surface.

Transdermine is a cream base with an added surface active agent. The blank cream did not have the surface active agent. In this case, there was no significant change in penetration when the surface active agent was included in the vehicle.

Table II gives preliminary observations on the result of pre-treating human skin with ether. There is a suggestion of increased penetration of C^{14} acetylsalicylic acid (in vitro) in skin pretreated with ether.

Table III also gives preliminary observations regarding pretreatment of skin with chloroform, ether, ethanol and water. Not enough observations are completed to draw conclusions but the differences, if they exist, are minimal.

Table IV indicates the effects of temperature on percutaneous absorption of C^{14} acetylsalicylic acid. These results indicate quite dramatic differences. More observations are being made.

PART II:

The anticholinergic (AHR-483) was obtained with a C^{14} label. This was applied to human leg and breast skin in vitro. A modified chamber method is used. This technique gives good, reproducible results. There have been some problems in technique but they have been overcome and we are quite confident in this method of measuring percutaneous absorption in vitro. The AHR-483 was applied to an area of 1 cm. diameter with environmental temperature of 37°C and a time period of 24 hours. During the 24 hours, 0.014% of applied counts penetrated to the bathing fluid on the corium side.

Intradermal injections of this agent (AHR-483) gives inhibition of sweating (in vivo) in man (forearm) with concentrations as low as 0.1 cc of 10^{-8} .

It takes 0.1 cc of 0.5% AHR-483 applied topically to the forearm of human volunteers to inhibit sweating. This inhibition will take place in 2-3 hours after topical application. The area covered in the topical application is 2-3 cm. diameter. The information obtained with the in vitro technique agrees fairly well with the in vivo technique in regard to percutaneous absorption.

Two to four mgm of AHR-483 given intramuscularly will give symptoms of dry mouth, difficulty in urination and possibly pupillary changes. However, topical application of 200 mgm of this agent at a given time and under occlusive (Saran) dressings will not give rise to symptoms of dry mouth or difficulty of urination. Again, this agrees with the other in vitro and in vivo data data regarding absorption of this agent.

All in vivo work with AHR-483 was done with human volunteers in the 20-40 year old age group.

A few preliminary studies indicate that AHR-483 will inhibit the development of miliaria. The miliaria is induced with occlusive dressing (Saran) for 16 hours. Part of the forearm is covered with 0.5% AHR-483 and the other part is covered with the base (water) only. The area is wrapped with Saran for 16 hours. The areas are compared for the presence and severity of miliaria. We have only done this with 2 subjects but the results are quite clear. The area treated with the anticholinergic (AHR-483) does not develop miliaria. This work was done on one young adult female and one young adult male.

PART III:

The object of this project is to study the function of the stratum corneum as a reservoir for topically applied drugs. We have reason to believe that drugs may remain in the epidermis for as long as fourteen days after original application. At present we are using physiological phenomena as markers for the continued presence of the drug in the epidermis. Topical steroids when applied under Saran Wrap show areas of vasoconstriction whilst nicotinic acid and its derivatives show vasodilatation. When Saran wrapping is repeated at various intervals after the original application of the drug, the physiological marker recurs thus indicating the presence of the drug somewhere in the epidermis during that period of time.

In a group of 167 experiments on 53 human volunteers we have been able to demonstrate the reservoir effect in over 90%. The duration of the reservoir varies widely from 2 to 17 days with an average of 7 days.

At present, we are investigating the various factors influencing the appearance or non-appearance of the reservoir effect.

Factors influencing the development of the reservoir:

- A) The minimal dose of the drug producing the physiological marker in the subject Figure 1.
- B) The duration of the occlusion with Saran Wrap. Figure 2.
- C) The dose of the drug applied. It appears that the best dose is at least 100 times the minimal dose needed to produce the marker but there are such wide variations here that at present the results are by no means clear.

There also appear to be many adverse factors of which the most important appear to be hirsutes on the experimental area and the degree of sweating that takes place under Saran. The former is being investigated by

experiments on shaved and unshaved areas in the same subject, and the latter by direct measurements of sweating with preweighed swabs placed under the Saran. It appears at present that the vital factor is the degree of sweating which leads to spreading of the steroid on the skin and thus to a lower concentration per unit area of skin.

Experiments to determine the actual site of the reservoir have been in two parts. First, if a dose of steroid which would be expected to produce a reservoir when applied topically is injected intradermally no reservoir effect is seen. Second, if after a reservoir has been established the stratum corneum is stripped by repeated applications of Scotch tape, it can be shown that the reservoir has been destroyed, nor can a reservoir be established in an area where the stratum corneum has been stripped prior to the application of the drug. These facts suggest that the reservoir is in the stratum corneum but there are difficulties in reading the physiological markers after stripping and experiments are in progress using C^{14} labelled steroids to more accurately delineate the site.

Sensitivity (Minimum dilation of Fluocinolone Acetonide Producing Vasoconstriction)

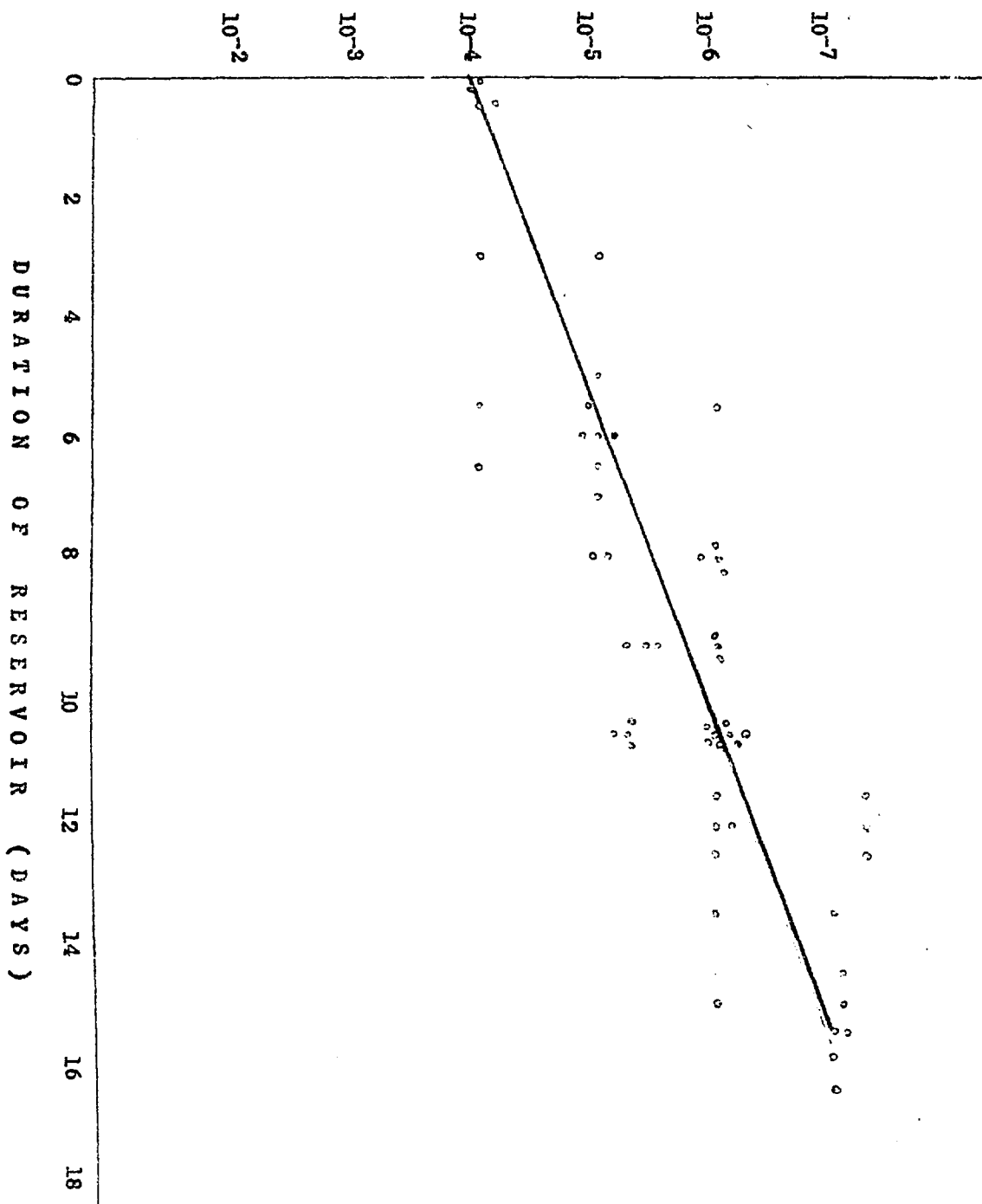


FIGURE 1

FIGURE 2

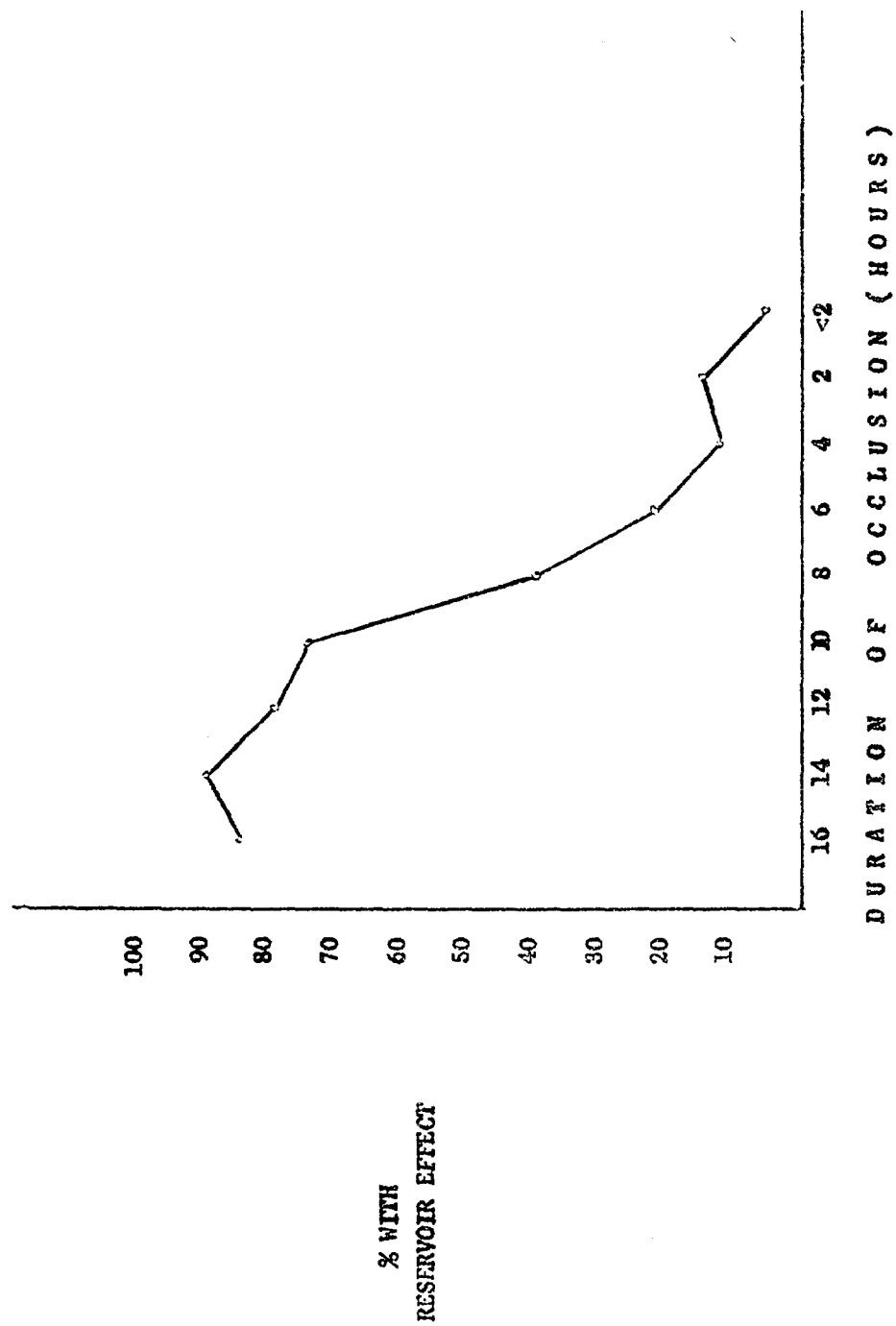


TABLE I

PERCUTANEOUS ABSORPTION OF LAURIC ACID - C¹⁴

Vehicle	Amount Applied in Mg	Per Cent Recovered at 24 Hrs	Average Penetration Mg/Cm ² /Hr	Blank Cream Transdermine
Blank Cream	5.45	0.17	48.7×10^{-5}	1.6
Transdermine	5.45	0.11	30.9×10^{-5}	
Blank Cream	2.73	0.14	20.4×10^{-5}	1.8
Transdermine	2.73	0.11	16.8×10^{-5}	
Blank Cream	0.55	0.23	6.5×10^{-5}	3.8
Transdermine	0.55	0.06	1.7×10^{-5}	
Blank Cream	0.22	0.20	2.38×10^{-5}	1.9
Transdermine	0.22	0.11	1.28×10^{-5}	

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TABLE II

PERCUTANEOUS ABSORPTION -- EFFECT OF SOLVENT PRETREATMENT
OF EXCISED HUMAN LEG SKIN ON THE PENETRATION
OF C¹⁴ ACETYLSALICYLIC ACID

37° C.	
**Treatment	Mg/*Cm ² /Hr.
Ether	3.35×10^{-3}
Control	0.71×10^{-3}

**15 min. immersion without agitation
*Areas by radiography and planimeter

x,(1)

TABLE III

PERCUTANEOUS ABSORPTION - EFFECT OF SOLVENT PRETREATMENT
OF EXCISED HUMAN LEG SKIN ON THE PENETRATION
OF C¹⁴ ACETYSALICYLIC ACID

37° C.	
**Treatment	Mg/Cm ² */Hr.
Chloroform	1.36 x 10 ⁻⁶
Ether	1.06 x 10 ⁻⁶
Ethanol	0.77 x 10 ⁻⁶
Water	2.92 x 10 ⁻⁶
Control	0.88 x 10 ⁻⁶

**30 min. immersion without agitation.

*Areas by radiography and planimeter

x1,(1)

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T A B L E I V

PERCUTANEOUS ABSORPTION
FRESH VS FROZEN LEG SKIN - PENETRATION
ACETYLSALICYLIC ACID C¹⁴

Temp. °C	10 ⁻⁶ Mg/Cm ² /Hr (Ave. for 5 hours)	
	Fresh	Frozen
5	1.32	0.73
22	96	4.4
37	810	180

xlii,xviii,(2)

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